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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,912	10/08/2004	Osvaldo A Flores	21080P	6208

210 7590 07/09/2007
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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
07/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,912	FLORES ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**.. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-21 and 27-43* is/are pending in the application.

4a) Of the above claim(s) *27 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,28,29,31-38 and 40-42* is/are rejected.

7)☒ Claim(s) *21,39 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/8/04, 7/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 18-21 and 27-43 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of Group II (of the May 9, 2007 restriction requirement), and the species wherein the replicon comprises SEQ ID NO: 2 (or a modified version thereof) and wherein the modification is a replacement of the NS5B protein coding sequence with that of a clinical isolate in the reply filed on May 29, 2007 is acknowledged. The traversal is on the ground(s) that there would be no undue burden on the examination of multiple Groups. This is not found persuasive because the examination of each of the various embodiments would require separate searches. Moreover, it is noted that the present restriction requirement is imposed under the PCT standard for Unity of Invention. It was determined that unity was lacking in the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 27 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 29, 2007.

4. Claims 18-21, 28, 29, and 31-43 are under consideration.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on October 8, 2004, and on July 27, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

The foreign reference DE 199 15 178 cited in the July 27, 2005 IDS is in a foreign language, and is not accompanied by an English translation or abstract. The reference has therefore been considered to the extent of the disclosure of the Search Report submitted on July 27, 2005.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 40 purports to depend from itself. As the claim depends from itself, it is not clear what the claim is further limiting to. The claim is therefore indefinite. Claims 41 and 42 depend from claim 40 and are therefore also indefinite.

For the purposes of this action, these claims are treated as though claim 40 depended from claim 39.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 18 is rejected under 35 U.S.C. 102(e) as being anticipated by De Francesco et al. (WO 02/059321). This claim is drawn to an HCV replicon comprising a beta-lactamase reporter, and lacking an antibiotic resistance gene. Such a replicon is disclosed by the reference. In particular, the reference teaches an HCV replicon comprising a reporter. Claims 5 and 6. The specification teaches that the reporter may be one of five exemplary reporters, including beta-lactamase. The reference therefore anticipates the indicated claim.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 18-20, 28, 29, 31-34, 37, and 38 rejected under 35 U.S.C. 103(a) as being unpatentable over De Francesco (WO 02/059321) in view of WO 01/89364 (of record in the Office action of May 2007) and of Rice et al. (6,297,003); and further in view of Melnick et al. (U.S. 6,063,562) and Li et al. (U.S. 2004/0018529). Claims 18 has been described above. The remaining claims are drawn to an HCV replicon comprising at lest two regions, wherein at least one of the regions comprises the 3' UTR from HCV subtype 1a. Claims 20, 21, and 31-38

require that the replicon comprises a second region consisting of a non-structural region from a clinical isolate of HCV. Claims 28, 29, 33, 34, 37, and 38 require that the replicon comprises a beta-lactamase reporter sequence, with claims 29, 34, and 38 additionally requiring that the replicon does not comprises a gene for resistance to an agent inhibiting cell growth (e.g. and antibiotic resistance gene). Claims 31 and 32 require that the non-structural region comprises an HCV NS5B polymerase.

As was described above, De Francesco teaches an HCV replicon comprising a reporter, such as beta-lactamase. Claims 5 and 6, and page 12. The reference also indicates that the replicon may independently include reporter or selection (i.e. sequences coding for resistance to growth inhibition agents) sequences, and therefore indicates that a replicon comprising one of the two need not include the other. See e.g., pages 11, lines 22-26. The reference also teaches that the replicons comprise an HCV 3' UTR sequence, and indicates that any such sequence may be used. Page 10, lines 23-30. The reference also indicates that the non-structural protein sequences used in the replicon may include proteins, including NS5B proteins, from different HCV strains. Pages 10-11. However, the reference does not teach or suggest the use of a HCV 3' UTR sequence from an HCV subtype 1a sequence, or specify the use of an NS5B protein from a clinical isolate.

Rice teaches the sequences of several HCV 3' UTRs, including the sequences of several variants of the HCV 1a isolate H77. See e.g., Figure 3, and column 11 (lines 20-25). The reference also indicates that such sequences would be useful for the construction of HCV replicons which could be used for screening for inhibitors of HCV replication. Columns 21 (lines 23-33) and 30 (lines 11-14). From these teachings, it would have been obvious to those of

ordinary skill in the art to use the 3' UTRs of Rice for the production of HCV replicons as suggested by De Francesco. Those of ordinary skill in the art would have been motivated to make such a substitution because the art indicates that the 3' UTRs of Rice are functional equivalents for the sequences provided in De Francesco. See e.g., MPEP 2144.06. Those of ordinary skill in the art would have had a reasonable expectation of success in making such substitutions based on the indication of De Francesco that any HCV 3' sequence could be used, and suggestion of the use of the 1a sequences in Rice.

Rice also does not teach or suggest the use of a sequence encoding an HCV NS5B protein from a clinical isolate. However, as was indicated above, De Francesco does suggest the use of NS5B sequences from different strains. In addition, the WO 01/89364 reference also provides teachings relating to HCV replicons, and indicates both that the replicons may comprise sequence form any HCV subtype (pages 20-21), and that the proteins encoded by the replicons may be from different isolates of HCV, including embodiments wherein one of the proteins in the encoded polyprotein is from a different subtype or strain. Pages 17 (lines 21-26) and 23 (lines 31-34). While the reference does not specifically teach the insertion of nucleotide sequences from clinical isolates, such would have been obvious to those of ordinary skill in the art from the teachings found therein. For example, the reference teaches that the replicons may be used to screen for anti-viral drugs, and indicates that wild-type forms of the targets for such drugs should be used. Page 32, lines 26-30. The reference also states "in a chronically infected individual, changes in the virus population occur over time…; and these changes may have important consequences for disease." Page 7. Moreover, other teachings in the art indicate that those of ordinary skill in the art would be particularly concerned with the identification of drugs that are

effective against clinical isolates of pathogens, or the development of resistance in target pathogenic populations that change over time. See e.g., U.S. 6,063,562 column 11(lines 6-13); and U.S. 2004/0018529, paragraph [0009]. While the teachings of these two references are directed to other enzymes, or to HIV enzymes, those of ordinary skill in the art of treating HCV would have looked to such teachings as similar problems would be seen with HCV as indicated by the teachings of WO 01/89364. Thus, based on the teachings of the cited references, and the knowledge in the art, it would have been obvious to those of ordinary skill in the art to have substituted NS5B proteins from HCV clinical isolates into an HCV replicon for the purpose of screening for inhibitors effective against such isolates, or for the detection of anti-viral resistance in such isolates. The combined teachings of these references therefore render the claimed inventions obvious.

12. Claims 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Francesco in view of Rice, WO 01/89364, Melnick, and Li as applied to claims 18-20, 28, 29, 31-4, 37, and 38 above, and further in view of Hawkins et al. (U.S. 5,783,669). These claims describe the previously described replicons as further comprising the presence of silent modifications to the replicon's nucleotide sequence which result in the presence of restriction sites not present in a naturally occurring HCV.

The teachings of De Francesco have been described above. This reference teaches the making of adaptive mutations to the replicon sequences, as well as combining such mutations to other mutations that do no inhibit replicon activity. Moreover, WO 01/89364 teaches both the substitution of a single protein within the replicon, and indicates that such may be accomplished

by modification of the replicon sequence to include restriction sites convenient for subsequence engineering. Pages 23 (lines 31-34) and 22 (lines 20-28). However, neither of these references specifically teaches the use of silent mutations for the creation of restriction sites up- and down-stream of a target region.

Nonetheless, such modifications would have been obvious to those of ordinary skill in the art. This is because, as is indicated by WO 01/89364e, it was known in the art to make such substitutions to optimize the insertion or cloning of sequences into viral or plasmid vectors. See also, Hawkins, column 5, lines 8-12. In addition, it is noted that the teachings of Hawkins specifically indicate that it was known by those of ordinary skill in the art to make such modifications through the use of silent nucleotide substitutions which take advantage of the redundancy in the genetic code. Id. In view of such knowledge in the art, and the suggestion by the teachings of the previously cited references to make chimeric HCV replicons wherein specific sequences are substituted for sequences of other HCV isolates, it would have been obvious to those of ordinary skill in the art to have used such a means for the cloning of the alternative HCV sequences into the chimeric replicons suggested by De Francesco and WO 01/89364. The combined teachings of these references therefore render the claimed inventions obvious.

Double Patenting

13. Applicant is advised that should claim 40 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight

difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the present case, claim 40 (treated as depending from claim 39) reads on a chimeric replicon of SEQ ID NO: 2 comprising a substitution of the NS5B coding region (or a portion thereof) of the sequence for the corresponding region of a clinical isolate. SEQ ID NO: 2 encodes a replicon comprising a β-lactamase reporter, and has no resistance gene. Claim 42 depends from claim 40, and purports to further limit the claim to embodiments wherein the replicon does not have a resistance gene. However, as SEQ ID NO: 2 does not contain a resistance gene, claim 42 is merely describing an inherent feature of the replicon of SEQ ID NO: 2, and therefore of the modified form thereof of claim 40. Thus, claim 42 includes no additional limitations to those provided in claim 40, and therefore reads on the same group of inventions.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 18-20, 28, 29, 31-34, 37, and 38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9 and 10 of copending Application No. 10/543,633. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application read on particular replicons that meet the present claim limitations. See e.g., page 16 of the application (teaching that the BK replicon of SEQ ID NO: 4 is a chimeric replicon comprising a beta-lactamase reporter, no selection gene, and having an HCV 1a 3' UTR sequence, and comprising non-structural regions from a clinical isolate).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

16. No claims are allowed. The replicon of SEQ ID NO: 2 appears to be allowable over the prior art. Claim 21 is objected to for depending from a rejected claim. Claims 21, 39, and 43 are objected to for reading on non-elected inventions (i.e. SEQ ID NO: 2).

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Z. Lucas/
Patent Examiner, AU 1648